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# Aromatic Trifluoromethylselenolation via Pd-catalyzed C-H functionalization

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**Abstract:** The synthesis of trifluoromethylselenolated aromatic molecules is described via an auxiliary-assisted, palladium catalyzed, C-H bonds functionalization with trifluoromethyl tolueneselenosulfonate as reagent. The mono- or bis-products can be preferentially formed. Some mechanistic investigations were realized to better understand the reaction. This methodology was also extended to fluoroalkylselenyl groups.

## Introduction

Fluorinated compounds have gained these last decades a huge interest making of them, nowadays, staples products in large panel of various applications. Thus, fluorinated molecules can be found in materials<sup>[1]</sup> (polymers, batteries, portable devices, ...) as well as in life sciences<sup>[2]</sup> (agrochemicals, medicinal chemistry, biologic applications, ...). This growing attention is mainly due to the specific properties brought by fluorine to molecules.<sup>[3]</sup> In the objective to design specific compounds for dedicated applications, various fluorinated groups have been developed these last years in order to modulate conferred properties. In this quest, merging of heteroatoms with fluorinated moieties gave valuable results.<sup>[4]</sup> In particular, chalcogens have clearly distinguished themselves over the past years. Nevertheless, if CF<sub>3</sub>O<sup>[5]</sup> and CF<sub>3</sub>S<sup>[6]</sup> moieties were well documented and studied, the next chalcogen, namely selenium, is still little explored.<sup>[7]</sup>

However, selenium is an essential trace element for human physiology and biology.<sup>[8]</sup> Moreover, selenylated compounds find promising applications in various fields from materials to drug design.<sup>[9]</sup> Consequently, consideration for CF<sub>3</sub>Se substituent began to emerge these recent past years. Such an interest was recently reinforced by the promising results of a CF<sub>3</sub>Se-substituted nonsteroidal antiinflammatory derivative as potential anticancer agent.<sup>[10]</sup>

This led to the recent emergence of CF<sub>3</sub>Se chemistry and more particularly to the direct introduction of CF<sub>3</sub>Se group onto organic substrates.<sup>[7a, 11]</sup> Nevertheless, despite this growing interest, direct trifluoromethylselenolations are still limited and development of

new reactions is always required. More specifically, aromatic functionalization appears quite restricted to few strategies. Coupling reactions, using transition metals, with aromatic boronic acids,<sup>[12]</sup> halides<sup>[13]</sup> or diazonium salts<sup>[14]</sup> were well-documented. Few nucleophilic aromatic substitutions of diazonium salts or diaryliodonium salts were also described.<sup>[15]</sup> Reactions with Grignard reagents and electrophilic trifluoromethylselenolating reagent were performed.<sup>[16]</sup> Finally, visible-light mediated trifluoromethylselenolation of diazonium salts is also possible.<sup>[17]</sup> Nevertheless, all these approaches required pre-functionalization of the aromatic core to introduce the "leaving group". The direct C-H functionalization was less described and only through electrophilic aromatic substitution reactions of electron-rich arenes, with the regioselectivity issues of such reactions.<sup>[18]</sup> Visible-light-induced trifluoromethylselenolation restricted to nitrogen heteroarenes was also described.<sup>[19]</sup> These last years, transition metals C-H activation to induce aromatic functionalization was explored and well-documented.<sup>[20]</sup> Nevertheless, to this day no transition-metal catalyzed trifluoromethylselenolation of aromatic C-H bonds were described. Consequently, we decided to investigate such reactions.

## Results and Discussion

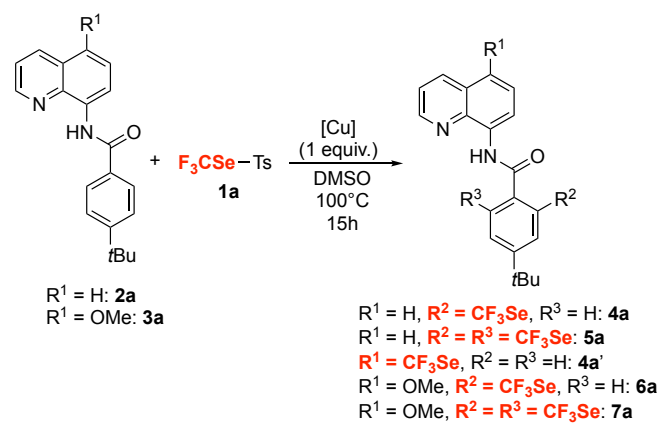
We recently described the synthesis of a stable and easy-to-handle reagent to perform various trifluoromethylselenolation reactions, namely trifluoromethyl tolueneselenosulfonate **1a**.<sup>[7a, 12b]</sup> Consequently, this reagent was used in this study.

A 8-aminoquinoline auxiliary-assisted trifluoromethylthiolation catalyzed with copper has been described in 2012 by Daugulis.<sup>[21]</sup> Therefore, such conditions have been first investigated with 8-aminoquinoline 4-*t*-butylbenzoic acid amide **2a** as model substrate (Table 1).

By using 8-amino-quinoline as a directing group (**2a**), only trifluoromethylselenolation of the C5 position of the quinoline part (**4a'**) was observed, in good yields, with CuBr and CuI (entries 1-2), as previously observed with CF<sub>3</sub>SeCl and Pd(OAc)<sub>2</sub>.<sup>[22]</sup> With

Cu(OAc)<sub>2</sub> as catalyst, **4a'** is always the lone obtained product, but in lower yield (entry 3). By precluding this position with a methoxy group (**3a**),<sup>[23]</sup> small amount of bis-trifluoromethylselenolation (**7a**) was formed in 15h or 24h (entries 4-5). In 48h, a mixture of mono-(**6a**) and bis-trifluoromethylselenolated (**7a**) products is observed with a slight better yield (entry 6). However, these compounds were mixed with several other unidentified fluorinated species. In view of these results, copper catalysis appeared to be not efficient enough to perform the targeted C-H trifluoromethylselenolation.

**Table 1.** Copper-catalyzed trifluoromethylselenolation of **2a**.

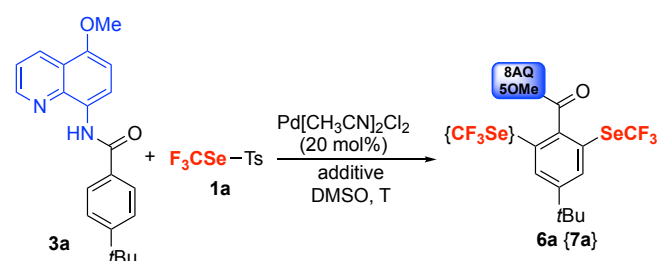


N°	[Cu]	R <sup>1</sup>	R <sup>1</sup> = H: <b>4a</b> / <b>5a</b> / <b>4a'</b> (%) <sup>[a]</sup> R <sup>1</sup> = OMe: <b>6a</b> / <b>7a</b> (%) <sup>[a]</sup>
1	CuBr	H	0 / 0 / 90
2	CuI	H	0 / 0 / 85
3	Cu(OAc) <sub>2</sub>	H	0 / 0 / 12
4	CuBr	OMe	0 / 7
5	CuBr <sup>[b]</sup>	OMe	0 / 9
6	CuBr <sup>[c]</sup>	OMe	8 / 15 <sup>[d]</sup>

[a] Yields determined by <sup>19</sup>F NMR with PhOCF<sub>3</sub> as internal standard, reported to **2a** or **3a**. [b] 24h. [c] 48h. [d] in mixture with other unidentified fluorinated products.

Due to these unsatisfactory results with copper, palladium catalyzed conditions were then envisaged. Starting from **2a**, a complex mixture of products arising from the expected C-H trifluoromethylselenolation, from the introduction of the CF<sub>3</sub>Se group at the C5 position of the quinoline core and from both reactions in same time was obtained. To circumvent this issue, 5-methoxy-8-amino-quinoline (**3a**) was then again considered as a directing group (Table 2).

**Table 2.** Palladium-catalyzed trifluoromethylselenolation of **2a**.<sup>[a]</sup>



N°	Additive (x equiv.)	Conditions	T (°C)	t (h)	<b>6a</b> (%) <sup>[b]</sup>	<b>7a</b> (%) <sup>[b]</sup>
1	PivOH (10)	N <sub>2</sub>	70	48	45	23
2 <sup>[c]</sup>	PivOH (10)	N <sub>2</sub>	70	48	24	4
3 <sup>[d]</sup>	PivOH (10)	N <sub>2</sub>	70	48	13	3
4	PivOH (10)	N <sub>2</sub>	70	24	44	15
5	PivOH (10)	N <sub>2</sub>	70	15	34	5
6	PivOH (1)	N <sub>2</sub>	70	24	44	10
7	PivOH (1)	N <sub>2</sub>	50	24	10	0
8	PivOH (1)	N <sub>2</sub>	25	24	4	0
9 <sup>[e]</sup>	PivOH (1)	N <sub>2</sub>	70	24	27	3
10 <sup>[f]</sup>	PivOH (1)	N <sub>2</sub>	70	24	15	0
11 <sup>[g]</sup>	PivOH (1)	N <sub>2</sub>	70	24	0	0
12	PivOH (1)	Air	70	24	46	25
<b>13</b>	-	<b>Air</b>	<b>70</b>	<b>24</b>	<b>49</b>	<b>20</b>
14 <sup>[h]</sup>	-	Air	70	24	45	15
15 <sup>[i]</sup>	-	Air	70	24	43	14
16 <sup>[j]</sup>	-	Air	70	24	27	8
17 <sup>[k]</sup>	-	Air	70	24	0	0
18 <sup>[l]</sup>	-	Air	70	24	0	0

[a] Standard conditions: **1a** (1 equiv., 0.1 mmol), **3a** (1 equiv.), Pd[CH<sub>3</sub>CN]<sub>2</sub>Cl<sub>2</sub> (20 mol%), DMSO (1 mL). [b] Yields determined by <sup>19</sup>F NMR with PhOCF<sub>3</sub> as internal standard, reported to **3a**. [c] DME as solvent. [d] DMF as solvent. [e] with Pd(OAc)<sub>2</sub> as catalyst. [f] with Pd(acac)<sub>2</sub> as catalyst. [g] with Co(OAc)<sub>2</sub> as catalyst. [h] with 10 mol% of [Pd]. [i] with 5 mol% of [Pd]. [j] with 2-(methylthio)aniline as directing group. [k] with pentafluoroaniline as directing group. [l] without catalyst. PivOH : pivalic acid.

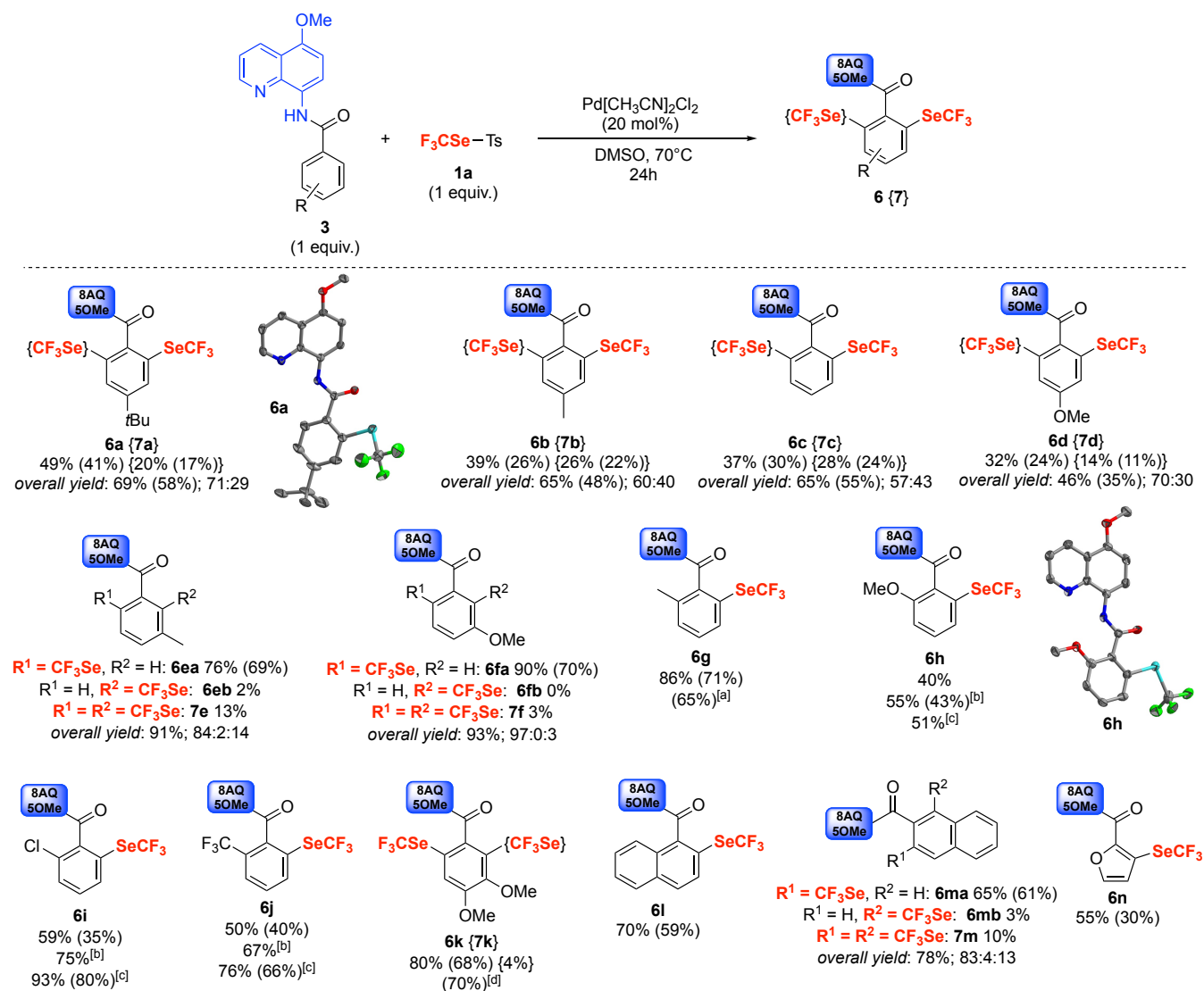
With Pd[CH<sub>3</sub>CN]<sub>2</sub>Cl<sub>2</sub> (20 mol%) as catalyst, in DMSO at 70°C and in presence of 10 equiv. of pivalic acid as additive, a good overall yield of expected products was obtained, in 48 h, with a total conversion of **1a** (yield reported to **1a** = 91%). A mixture (2:1) of mono-(**6a**) and bis-trifluoromethylselenolation (**7a**) was observed (entry 1). Use of DME (entry 2) or DMF (entry 3) as solvent appeared to be deleterious to the reaction. In 24h, similar yield of mono-adduct (**6a**) was formed but formation of the bis-adduct (**7a**) was decreased (entry 4). In 15h an overall drop of yields was then observed (entry 5). The use of only 1 equiv. of pivalic acid did not affect the results of reaction (entries 4, 6). By diminishing the temperature to 50°C or 25°C, a drastic drop of yields was noticed

(entries 7-8). The replacement of catalyst with Pd(OAc)<sub>2</sub> or Pd(acac)<sub>2</sub> was also deleterious for the reaction (entries 9-10). The change of metal by using Co(OAc)<sub>2</sub> as catalyst totally precluded the reaction (entry 11). An increase of the overall yield was observed under not controlled inert conditions (entry 12); same results as in first assay (entry 1) was achieved. Because the presence of pivalic acid seemed to induce purification issues, reaction was also carried out without additive and similar results were obtained (entry 13). Smaller amounts of catalyst (10 and 5

mol%) induced only slight decreases of yields (entries 14-15). Finally, two others directing group were also tested but with worse to no results (entries 16-17).

In view of these results, Pd[CH<sub>3</sub>CN]<sub>2</sub>Cl<sub>2</sub> (20 mol %), without pivalic acid, under air, at 70°C for 24h (entry 13) was selected as optimal conditions, the best yields being obtained in this case.

These conditions in hand, the scope of the reaction was then studied (Scheme 1).



**Scheme 1.** Scope of C-H trifluoromethylselenolation. Standard conditions: **1a** (1 equiv., 0.2 mmol), **3** (1 equiv.), Pd[CH<sub>3</sub>CN]<sub>2</sub>Cl<sub>2</sub> (20 mol%), DMSO (2 mL), 70°C, 24h. Yields determined by <sup>19</sup>F NMR with PhOCF<sub>3</sub> as internal standard, reported to **3**. In parentheses, isolated yields. [a] scale-up to 1 mmol. [b] 48h. [c] 120h. [d] scale-up to 1.5 mmol.

Similar results were obtained with methyl substituent (**3b**) or no substituent (**3c**) in place of tert-butyl (**3a**). The ratio mono (**6a-c**) / bis (**7a-c**) functionalization increases with the steric hindrance. With the methyl group in meta position (**3e**), C6 mono substituted product (**6ea**) is the main product, due to the steric hindrance of C2 position. When methyl group occupies one of the ortho position, only mono-trifluoromethylselenolation was performed

with excellent yield (**6g**). With methoxy group in para position, lower yields were observed, because of the electron-withdrawing effect of this substituent (**6d**, **7d**). This was confirmed by the dropped yield also obtained with OMe in ortho position (**6h**). However, when methoxy group is in meta position, i.e. in para position of C6, the mono-substituted product **6fa** is nearly the alone formed compound with excellent yield. This can be

rationalized by the mesomeric electron-donor effect of this group for the C6 position. Such a good result was confirmed with 3,4-dimethoxy substrate which provided nearly exclusively mono-trifluoromethylselenolated compound with good yield (**6k**). Ortho substituted substrates with electron-withdrawing moieties gave rise to lower yields (**6h-j**), compared to **6g**. Nevertheless, by increasing reaction times, higher yields were generally recovered (**6i-j**). Noteworthy, the reaction is compatible with the presence of a chlorine substituent (**6i**). Surprisingly, no significant kinetic amelioration was observed in case of OMe group (**6h**). To explain this fact, we assumed that a hydrogen bond between ortho-OMe and NH could contribute to restrain the conformation into a non-contributive form. This was consolidated by X-Rays structures determination of starting substrate **3h** and final product **6h**, which both confirmed the hydrogen bond (Figure 1), and by the downfield shifts in <sup>1</sup>H NMR of NH signals (see SI). In naphthyl series, good yields were obtained (**6l-m**). With C1-substituted naphthyl, only mono-trifluoromethylselenolation was performed (**6l**). In contrast, with C2- substituted naphthyl, mono-trifluoromethylselenolation in C3 position was the major observed product (**6ma**), but few amounts of C1 functionalization (**6mb**) and bis-trifluoromethylselenolation (**7m**) were also formed. Finally, a heteroatomic substrate was also engaged (**3n**). Thus, furan derivative was selectively trifluoromethylselenolated with satisfactory yield (**6n**).

The reaction was scaled-up for **6g** (285 mg, 1 mmol scale) and **6k** (500 mg, 1.5 mmol scale) with comparable results.

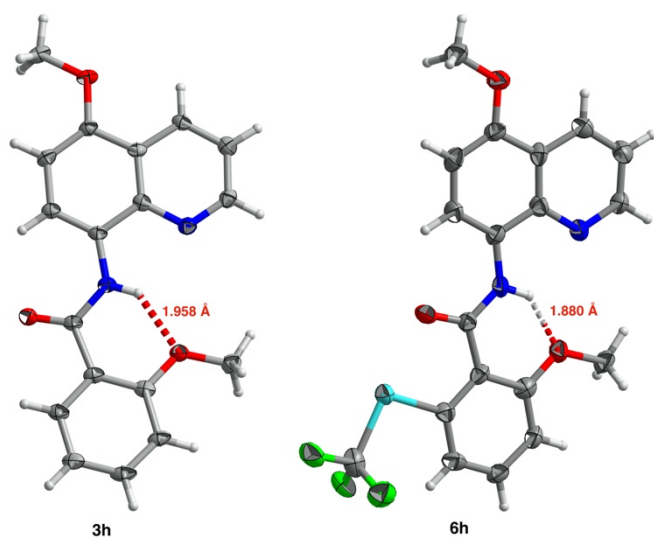
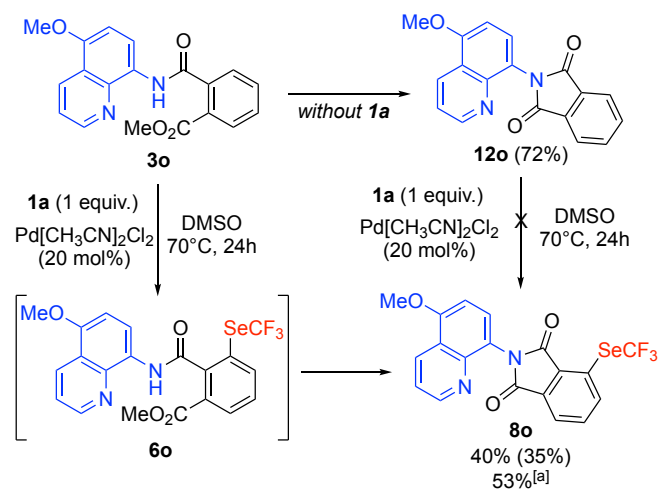


Figure 1. X-Ray crystal structures of **3h** and **6h**.

When ester substrate **3o** was engaged in this reaction, no expected product **6o** was obtained (Scheme 2). In this case, only phtalimide **8o** was formed with medium yield. This product arises certainly from cyclization between ester and NH functions of product **6o**. Cyclization of **3o** in conditions of reaction was demonstrated. The resulting phtalimide **12o** was engaged in C-H functionalization without success. Consequently, because **12o** cannot be trifluoromethylselenolated in our conditions, this cyclization constitutes an escape reaction consuming starting substrate and explains the medium yield observed. The yield was

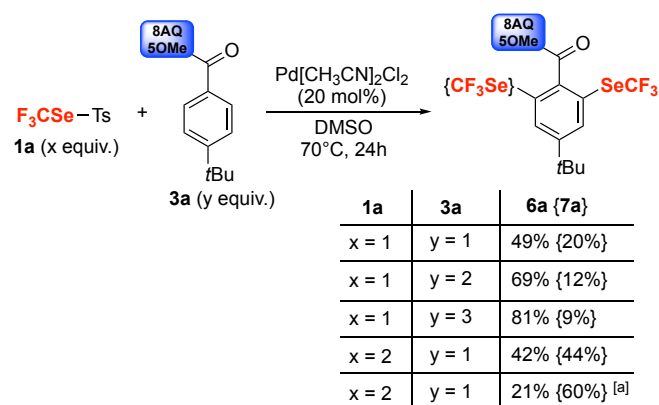
somewhat improved by using 2 equiv. of **1a** to foster the C-H functionalization.



Scheme 2. Formation of trifluoromethylselenolated phtalimide. Yields determined by <sup>19</sup>F NMR with PhOCF<sub>3</sub> as internal standard, reported to **3o**. In parentheses, isolated yields. [a] with 2 equiv. of **1a**.

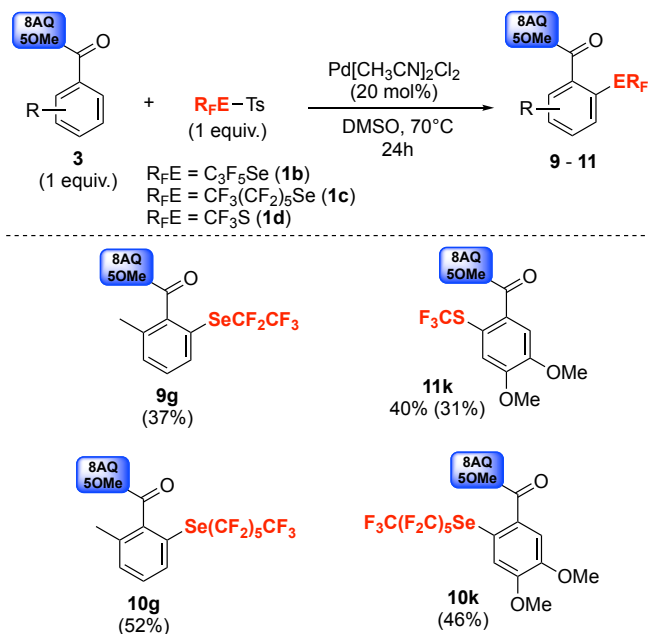
In order to favor the selective formation of mono- or bis-trifluoromethylselenolated product starting from non-ortho-substituted substrate **3**, the role of ratio **1a** / **3a** was investigated (Scheme 3).

By increasing the amount of **3a**, the formation of mono-trifluoromethylselenolated product (**6a**) could be significantly enhanced up to 81%. To favor the bis-trifluoromethylselenolated compound (**7a**), the quantity of reagent **1a** was also augmented. With 2 equivalents of **1a**, the yield of **7a** was ameliorated but less efficiently. However, with longer time reaction (72h instead of 24h), the amount of **7a** increases, letting suppose that the kinetic of bis-trifluoromethylselenolation would be slower.



Scheme 3. Role of ratio **1a** / **3a** on reaction. Yields determined by <sup>19</sup>F NMR with PhOCF<sub>3</sub> as internal standard. [a] 72h

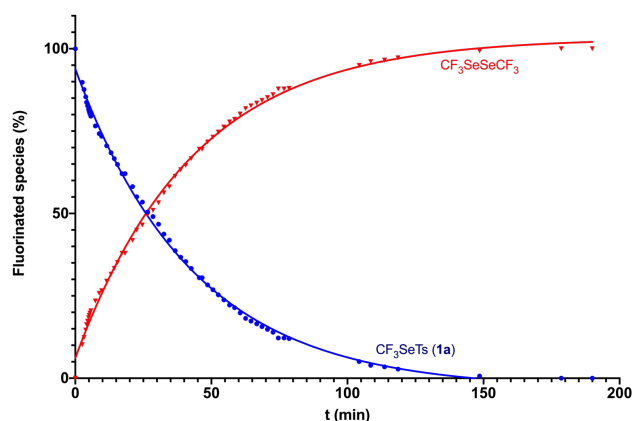
Higher fluorinated homologs (**1b-c**) and sulfur analog (**1d**) of **1a** were also previously synthesized.<sup>[12b, 24]</sup> Consequently, C-H perfluoroalkylselenolation and trifluoromethylthiolation reactions were also investigated (Scheme 4).



**Scheme 4.** Perfluoroalkylseleno(thio)lation. Yields determined by  $^{19}\text{F}$  NMR with  $\text{PhOCF}_3$  as internal standard, reported to **3**. In parentheses, isolated yields.

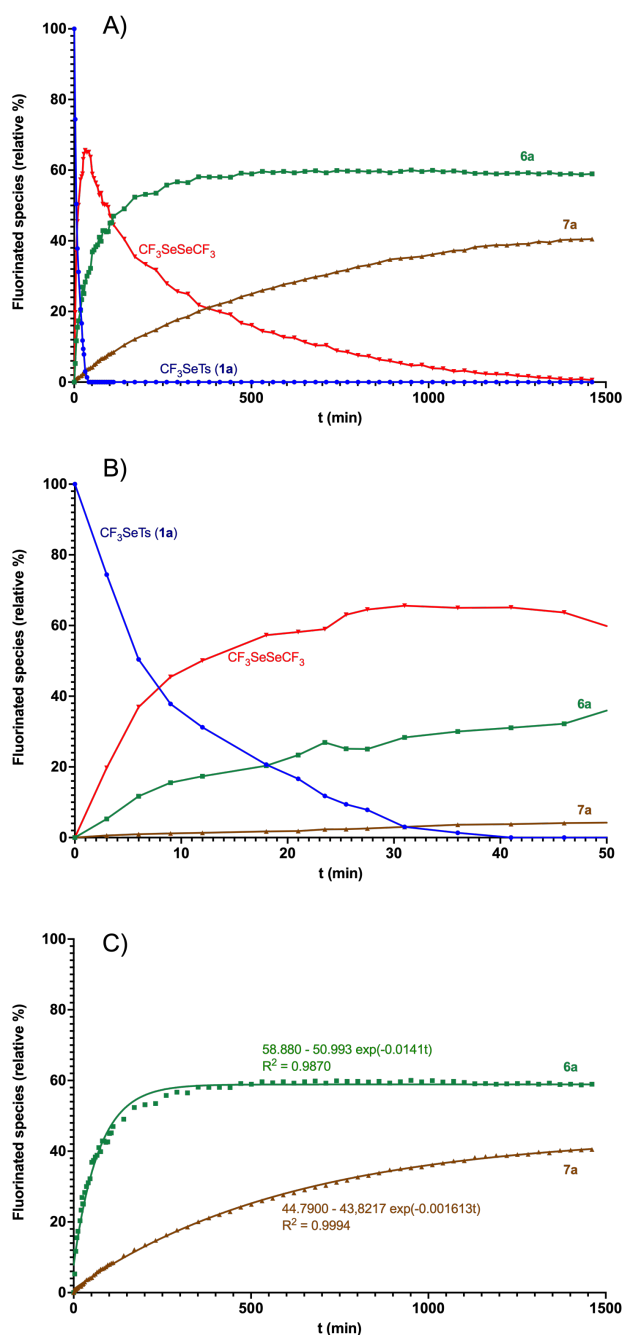
If medium to low yields were obtained with pentafluoroethyl (**9g**) derivative, maybe due to partial degradation of  $\text{CF}_3\text{CF}_2\text{Se}$  moiety, tridecafluorohexylselenolated compounds **10g** and **10k** were formed with satisfactory result. The reaction conditions were also applied to sulfur analog (**1d**). The expected trifluoromethylthiolated product **11k** was obtained with satisfactory yield, but lower than in Se series (**6k**).

Some investigations were performed to determine the reaction mechanism. A control reaction, without Pd catalyst (Table 2; entry 18), confirmed that the process required a metal catalysis. During our investigations to determine the optimal conditions, the formation of  $\text{CF}_3\text{SeSeCF}_3$  dimer was regularly highlighted by  $^{19}\text{F}$  NMR. In order to determine the origin of this dimer, the behavior of **1a** in DMSO at  $70^\circ\text{C}$  was monitored by  $^{19}\text{F}$  NMR (Figure 2). Reagent **1a** was rapidly degraded to quantitatively provide  $\text{CF}_3\text{SeSeCF}_3$ . This led to envisage that this dimer could also act as trifluoromethylselenolating reagent.



**Figure 2.** Monitoring by  $^{19}\text{F}$  NMR of **1a** in DMSO at  $70^\circ\text{C}$ . Symbols  $\bullet$  and  $\blacktriangledown$  are experimental points and lines are non-linear fits.

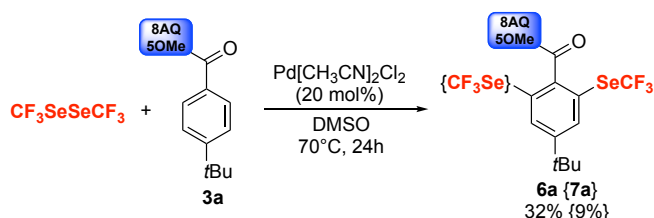
Monitoring of reaction by  $^{19}\text{F}$  NMR was also performed to see the species evolution during the process (Figure 3).



**Figure 3.** Monitoring by  $^{19}\text{F}$  NMR of reaction. A) Full monitoring. B) Zoom of first 50 minutes. C) Non-linear fits for **6a** and **7a**.

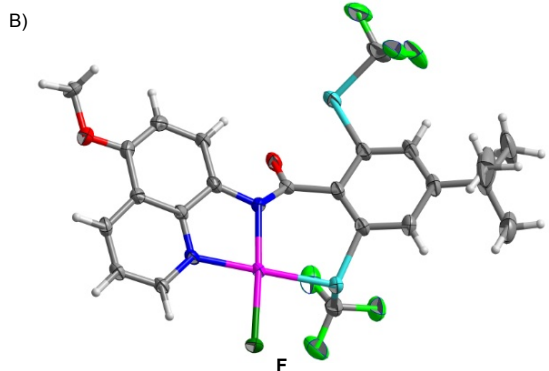
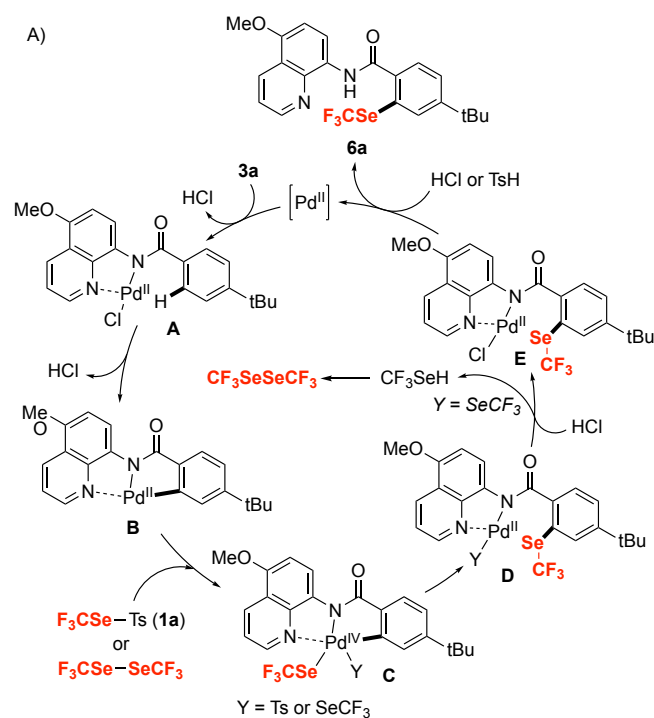
Degradation of **1a** and formation of  $\text{CF}_3\text{SeSeCF}_3$  appeared to be more rapid than in the degradation experiment (Figure 3B and Figure 2). As supposed previously, mono-trifluoromethylselenolation (**6a**) is faster than bis-trifluoromethylselenolation (**7a**). This was confirmed by the factor of 10 between rate constants arising from non-linear fits (Figure 3C).

The fast formation of  $\text{CF}_3\text{SeSeCF}_3$  led to suppose that this dimer would be the real trifluoromethylselenolating reagent in place of **1a**. Nevertheless, when dimer was preformed before the reaction, slight lower yields were obtained (Scheme 5). This result could let to suppose that **1a** could also play a little role in C-H trifluoromethylselenolation.



**Scheme 5.** Trifluoromethylselenolation with  $\text{CF}_3\text{SeSeCF}_3$ . Yields determined by  $^{19}\text{F}$  NMR with  $\text{PhOCF}_3$  as internal standard, reported to **3a**.

From these observations and literature,<sup>[25]</sup> the following mechanism can be proposed (Scheme 6A).

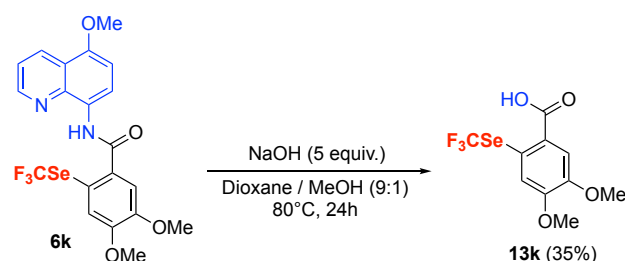


**Scheme 6.** Mechanism proposal.

Coordination of Pd(II) with bidentate directing-group aminoquinoline leads to intermediate **A**. This first species forms the palladacycle **B** which undergoes oxidative addition of trifluoromethylselenolating reagent **1a** or  $\text{CF}_3\text{SeSeCF}_3$  to afford the Pd(IV) species **C**. Reductive elimination affords the intermediate **D** with C-Se $\text{CF}_3$  bond formation. The palladium trifluoromethylselenide species (**D**,  $\text{Y} = \text{CF}_3\text{Se}$ ) reacts with HCl to provide the chloropalladium intermediate **E** and  $\text{CF}_3\text{SeH}$ . This step was confirmed by X-ray characterization of the species **F** (Scheme 6B). After acidification, the expected products **6a** is obtained and Pd(II) catalyst is regenerated.

Trifluoromethylselenol ( $\text{CF}_3\text{SeH}$ ) is readily oxidized to regenerate diselenide  $\text{CF}_3\text{SeSeCF}_3$ .<sup>[26]</sup> This is consolidated by good yields achieved whereas only 0.5 equiv. of  $\text{CF}_3\text{SeSeCF}_3$  can be formally formed from 1 equiv. of **1a** during the reaction. This oxidation step may be favored by the presence of air, which could explain the better results observed under air.

Finally, a non-optimized removal of the 5-methoxy-8-aminoquinoline directing group was performed in mild conditions<sup>[27]</sup> to provide the corresponding trifluoromethylselenolated acid **13k** (Scheme 7).



**Scheme 7.** Removal of directing group.

## Conclusion

With this work, trifluoromethyl tolueneselenosulfonate **1a** confirms its high efficiency as trifluoromethylselenolating reagent. After electrophilic, nucleophilic and radical reactions, it also shows its ability to easily perform palladium-catalyzed C-H trifluoromethylselenolation. The mono- and bis-functionalization can be favored depending on the conditions. These results open the way to the access of various trifluoromethylselenolated products for further applications. Furthermore, with this method, perfluoroalkylselenolation can also be realized, allowing, for instance, an access to unusual tridecafluoroheptylselenolated compounds. No doubt that these reagents should find their place in the toolbox of emerging fluorinated groups.

## Experimental Section

**Typical procedure for the C-H trifluoromethylselenolation.** To a 10 mL tube equipped with a magnetic stir bar are added  $\text{TsSeCF}_3$  (0.2 mmol, 1 equiv.), benzamide (0.2 mmol, 1 equiv.) and Pd catalyst (0.04 mmol, 0.2 equiv.) in dry DMSO (2 mL, 0.1 M). The tube is sealed, and the mixture is stirred at 70°C for 24h. Conversion is checked by  $^{19}\text{F}$  NMR with  $\text{PhOCF}_3$  as internal standard. The reaction mixture is partitioned between DCM and water, the combined organic layers are washed with water then brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated under moderate vacuum. The

crude residue is then purified by flash chromatography to afford the desired product.

<url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.2022#####">Deposition Number(s) 2060429 (for **3h**), 2060430 (for **6a**), 2065526 (for **6h**), 2065527 (for **F**) </url> contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service <url href="https://www.ccdc.cam.ac.uk/structures/?">www.ccdc.cam.ac.uk/structures</url>

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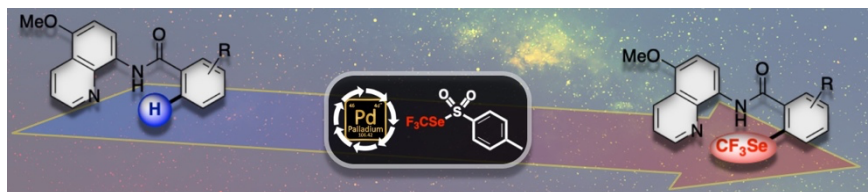
**Keywords:** Fluorine • Selenium • C-H functionalization • Trifluoromethylselenolation • Trifluoromethylselenosulfonate

- [1] a) M. Pagliaro, R. Ciriminna, *J. Mater. Chem.* **2005**, *15*, 4981-4991; b) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496-3508; c) D. Chopra, T. N. G. Row, *CrystEngComm* **2011**, *13*, 2175-2186; d) *Fascinating Fluoropolymers and Their Applications* (Eds.: B. Ameduri, S. Fomin), Elsevier, Amsterdam, Netherlands, **2020**; e) B. Ameduri, *Macromol. Chem. Phys.* **2020**, *221*, 1900573.
- [2] a) M. Cheng, C. Guo, M. L. Gross, *Angew. Chem. Int. Ed.* **2020**, *59*, 5880-5889; *Angew. Chem.* **2020**, *132*, 5932-5942; b) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467; c) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422-518; d) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822-5880; e) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797-11819; f) J. Han, A. M. Remete, L. S. Dobson, L. Kiss, K. Izawa, H. Moriwaki, V. A. Soloshonok, D. O'Hagan, *J. Fluorine Chem.* **2020**, *239*, 109639; g) B. M. Johnson, Y.-Z. Shu, X. Zhuo, N. A. Meanwell, *J. Med. Chem.* **2020**, *63*, 6315-6386; h) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633-10640.
- [3] a) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2013**; b) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3-11.
- [4] *Emerging Fluorinated Motifs: Synthesis, Properties and Applications* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**.
- [5] a) F. R. Leroux, B. Manteau, J.-P. Vors, S. Pazenok, *Beilstein J. Org. Chem.* **2008**, *4*, 13; b) A. Tlili, F. Toulgoat, T. Billard, *Angew. Chem. Int. Ed.* **2016**, *55*, 11726-11735; *Angew. Chem. Int. Ed.* **2016**, *128*, 11900-11909; c) T. Besset, P. Jubault, X. Pannecoucke, T. Poisson, *Org. Chem. Front.* **2016**, *3*, 1004-1010; d) J. W. Lee, K. N. Lee, M.-Y. Ngai, *Angew. Chem. Int. Ed.* **2019**, *58*, 11171-11181; *Angew. Chem.* **2019**, *131*, 11289-11299.
- [6] a) F. Toulgoat, T. Billard in *Modern Synthesis Processes and Reactivity of Fluorinated Compounds: Progress in Fluorine Science* (Eds.: H. Groult, F. Leroux, A. Tressaud), Elsevier Science, London, United Kingdom, **2017**, pp. 141-179; b) A.-L. Barthelemy, E. Magnier, G. Dagousset, *Synthesis* **2018**, *50*, 4765-4776; c) M. Hamzehloo, A. Hosseinian, S. Ebrahimiasl, A. Monfared, E. Vessally, *J. Fluorine Chem.* **2019**, *224*, 52-60; d) F.-G. Zhang, X.-Q. Wang, Y. Zhou, H.-S. Shi, Z. Feng, J.-A. Ma, I. Marek, *Chem. Eur. J.* **2020**, *26*, 15378-15396; e) D. E. Yerien, S. Barata-Vallejo, A. Postigo, *J. Fluorine Chem.* **2020**, *240*, 109652; f) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731-764.
- [7] a) T. Billard, F. Toulgoat in *Emerging Fluorinated Motifs: Synthesis, Properties and Applications* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 691-721; b) Y. Wang, Z. Ye, H. Zhang, Z. Yuan, *Adv. Synth. Catal.* **2021**, *363*, 1835-1854.
- [8] a) EFSA Panel on Dietetic Products, Nutrition and Allergies., *EFSA Journal* **2014**, *12*, 3846; b) European Food Safety Authority, *EFSA Supporting Publications* **2017**, *14*, e15121E; c) M. P. Rayman, *Lancet* **2000**, *356*, 233-241.
- [9] a) L. V. Romashov, V. P. Ananikov, *Chem. Eur. J.* **2013**, *19*, 17640-17660; b) Q. Li, Y. Zhang, Z. Chen, X. Pan, Z. Zhang, J. Zhu, X. Zhu, *Org. Chem. Front.* **2020**, *7*, 2815-2841; c) W. Guo, Y. Fu, *Chem. Eur. J.* **2020**, *26*, 13322-13331; d) G. Mugesh, W.-W. du Mont, H. Sies, *Chem. Rev.* **2001**, *101*, 2125-2180; e) N. Singh, A. C. Halliday, J. M. Thomas, O. V. Kuznetsova, R. Baldwin, E. C. Y. Woon, P. K. Aley, I. Antoniadou, T. Sharp, S. R. Vasudevan, G. C. Churchill, *Nat. Commun.* **2013**, *4*, 1332; f) J. B. T. Rocha, B. C. Piccoli, C. S. Oliveira, *ARKIVOC* **2017**, 457-491; g) *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments* (Eds.: V. K. Jain, K. I. Priyadarsini), Royal Society of Chemistry, Croydon, UK, **2018**; h) Z. Chen, H. Lai, L. Hou, T. Chen, *Chem. Commun.* **2020**, *56*, 179-196; i) A. D. Landgraf, A. S. Alsegiani, S. Alaql, S. Thanna, Z. A. Shah, S. J. Sucheck, *ACS Chem. Neurosci.* **2020**, *11*, 3008-3016; j) V. Alcolea, S. Pérez-Silanes, *Eur. J. Med. Chem.* **2020**, *206*, 112673.
- [10] X. He, M. Zhong, S. Li, X. Li, Y. Li, Z. Li, Y. Gao, F. Ding, D. Wen, Y. Lei, Y. Zhang, *Eur. J. Med. Chem.* **2020**, *208*, 112864.
- [11] X.-H. Yang, D. Chang, R. Zhao, L. Shi, *Asian J. Org. Chem.* **2021**, *10*, 61-73.
- [12] a) Q. Lefebvre, R. Pluta, M. Rueping, *Chem. Commun.* **2015**, *51*, 4394-4397; b) Q. Glenadel, C. Ghiazza, A. Tlili, T. Billard, *Adv. Synth. Catal.* **2017**, *359*, 3414-3420; c) C. Ghiazza, A. Tlili, T. Billard, *Molecules* **2017**, *22*, 833-841.
- [13] a) A. Haas, H.-U. Krächter, *Chem. Ber.* **1988**, *121*, 1833-1840; b) C. Chen, L. Ouyang, Q. Lin, Y. Liu, C. Hou, Y. Yuan, Z. Weng, *Chem. Eur. J.* **2014**, *20*, 657-661; c) M. Aufiero, T. Sperger, A. S. K. Tsang, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2015**, *54*, 10322-10326; *Angew. Chem.* **2015**, *127*, 10462-10466; d) Q. Tian, Z. Weng, *Chin. J. Chem.* **2016**, *34*, 505-510; e) A. B. Dürr, H. C. Fisher, I. Kalvet, K.-N. Truong, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 13431-13435; *Angew. Chem.* **2017**, *129*, 13616-13620; f) J.-B. Han, T. Dong, D. A. Vicic, C.-P. Zhang, *Org. Lett.* **2017**, *19*, 3919-3922.
- [14] C. Matheis, V. Wagner, L. J. Goossen, *Chem. Eur. J.* **2016**, *22*, 79-82.
- [15] T. Dong, J. He, Z.-H. Li, C.-P. Zhang, *ACS Sustain. Chem. Eng.* **2018**, *6*, 1327-1335.
- [16] a) L. M. Yagupol'skii, V. G. Voloshchuk, *Russ. J. Gen. Chem.* **1967**, *37*, 1463-1465; b) Q. Glenadel, E. Ismalaj, T. Billard, *Eur. J. Org. Chem.* **2017**, 530-533.
- [17] C. Ghiazza, V. Debrauwer, C. Monnereau, L. Khrouz, M. Médebielle, T. Billard, A. Tlili, *Angew. Chem. Int. Ed.* **2018**, *57*, 11781-11785; *Angew. Chem.* **2018**, *130*, 11955-11959.
- [18] a) L. M. Yagupol'skii, V. G. Voloshchuk, *Russ. J. Gen. Chem.* **1966**, *36*, 173-174; b) V. G. Voloshchuk, L. M. Yagupol'skii, G. P. Syrova, V. P. Bystrov, *Russ. J. Gen. Chem.* **1967**, *37*, 105-108; c) L. M. Yagupol'skii, V. G. Voloshchuk, *Russ. J. Gen. Chem.* **1968**, *38*, 2426-2429; d) A. Haas, M. Lieb, S. Schwederski, *Rev. Roum. Chim.* **1987**, *32*, 1219-1224; e) Q. Glenadel, E. Ismalaj, T. Billard, *J. Org. Chem.* **2016**, *81*, 8268-8275; f) Q.-Y. Han, C.-L. Zhao, T. Dong, J. Shi, K.-L. Tan, C.-P. Zhang, *Org. Chem. Front.* **2019**, *6*, 2732-2737.
- [19] A. De Zordo-Banliat, L. Barthélémy, F. Bourdreux, B. Tuccio, G. Dagousset, B. Pégot, E. Magnier, *Eur. J. Org. Chem.* **2020**, *2020*, 506-509.
- [20] a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147-1169; b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315-1345; c) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009; *Angew. Chem.* **2012**, *124*, 9092-9142; d) *C-H Bond Activation and Catalytic Functionalization II* (Eds.: P. H. Dixneuf, H. Doucet), Springer International Publishing, Switzerland, **2016**; e) *Strategies for Palladium-Catalyzed Non-Directed and Directed C-H Bond Functionalization* (Eds.:



- A. R. Kapdi, D. Maiti), Elsevier, Amsterdam, Netherlands, **2017**; f) R. Sharma, U. Sharma, *Catal. Rev.: Sci. Eng.* **2018**, *60*, 497-565; g) *Remote C-H Bond Functionalizations: Methods and Strategies in Organic Synthesis* (Eds.: D. Maiti, S. Guin), WILEY - VCH, Weinheim, Germany, **2021**; h) L. K. Boerner, *Chem. Eng. News* **2021**, *99*, 28-33.
- [21] L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237-18240.
- [22] C. Ghiazza, M. Ndiaye, A. Hamdi, A. Tlili, T. Billard, *Tetrahedron* **2018**, *74*, 6521-6526.
- [23] G. He, S.-Y. Zhang, W. A. Nack, Q. Li, G. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 11124-11128.
- [24] C. Ghiazza, C. Monnereau, L. Khrouz, T. Billard, A. Tlili, *Synthesis* **2019**, *51*, 2865-2870.
- [25] M. Iwasaki, Y. Tsuchiya, K. Nakajima, Y. Nishihara, *Org. Lett.* **2014**, *16*, 4920-4923.
- [26] V. K. Jain in *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments*, The Royal Society of Chemistry, Croydon, UK, **2018**, pp. 1-33.
- [27] V. Theodorou, G. Paraskevopoulos, K. Skobridis, *ARKIVOC* **2015**, 101-112.

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Trifluoromethylselenenolation of arenes was performed through a metal-catalyzed C-H functionalization. This pallado-catalyzed reaction was based on the use of 5-methoxy-8-amino-quinoline as directing group and trifluoromethyl tolueneselenosulfonate as trifluoromethylselenenolating reagent. This method was also extended to fluoroalkylselenenolation reactions.

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